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EXAMINER	
O DELL, DAVID K	

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1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,217	TAJIMI ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7 and 19-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7 and 19-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *19 October 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-5, 7, 19-26 are pending in the current application.

2. This is application is a national stage of PCT/EP2003/013452, filed November 28, 2003, which claims the priority of European Union Application EP 02027528.5, filed December 9, 2002.

Response to Arguments

3. Applicant's arguments filed October 19, 2007 have been fully considered but they are not fully persuasive. With respect to the interview, the examiner had previously indicated that removal of the 112 2nd paragraph rejections based on applicant's remarks and subsequent amendments would be forthcoming, thus the remarks on pgs. 9-14 are moot and these rejections are herby withdrawn. However with respect to the interview and the favorable disposition of the examiner towards the method of treating pain, the applicant is under the misapprehension that the treatment of pain was indicated allowable. The allowability was contingent upon the submission of in-vivo data, which Mr. Madge indicated would be provided in the response. The examiner has provided several reasons (with references), to show the lack of correlation of these assays for the treatment of pain based on the paucity of data provided (cell based assays). It should be clear that the assays of the specification, save the cell based capsaicin antagonism, are entirely prophetic. Mr. Madge had indicated that the compounds were tested in the numerous prophetic animal assays in the instant specification, and the examiner was under the impression that such data would be made available to him. In the absence of such data, the examiner maintains the current rejections for the treatment of pain. The examiner indicated that treatment of pain was a valid goal of TRPV1 antagonist development, but fell short of indicating

allowability. With respect to the under and 112 1st paragraph for enablement on the remainder of the disease the rejections are maintained for the reasons of record. With respect to the treatment of a "urological disorder", which the applicant seems to argue as only encompassing overactive bladder based on the exhibits, all of the arguments and references only show that capsaicin antagonists are able to reduce the capsaicin induced contraction of the rat urinary bladder, Exhibit W. Again as the examiner pointed out previously capsaicin is not the endogenous ligand for TRPV1, and the ligand is currently unknown (see the previous discussion). Nonetheless the examiner submits yet more information regarding the role of VR1 antagonists in overactive bladder treatment:

"VR1 knockout mice have no noticeable problems with micturition control,[45,46] suggesting that under physiological conditions the voiding reflex arc does not depend on vanilloid-sensitive nerves..... The role that vanilloid-sensitive nerves have in the physiological control of storage and voiding remains to be identified..... In conclusion, intravesical vanilloid treatment represents an attractive therapeutic approach that deserves further attention. So far, it has failed to become an established treatment; many patients found capsaicin painful despite attempts to make it more tolerable by the coadministration of local analgesics. Although resiniferatoxin seems to be superior to capsaicin in terms of its tolerability profile, its clinical efficacy has yet to be adequately explored. We hope that further scientific investigation into novel vanilloids and the mechanisms by which they work will eventually lead to useful therapies for the treatment of urinary bladder disorders." Arpad Szallasi and Clare J Fowler "After a decade of intravesical vanilloid therapy: still more questions than answers" THE LANCET Neurology Vol 1 July **2002** 167-172.

"The results of the two available placebo-controlled clinical trials are conflicting: one suggests clinical utility [73], whereas the other does not demonstrate any advantage from TRPV1 desensitization [74].....In summary, TRPV1-deficient mice and first-generation TRPV1 antagonist results need to be confirmed using new-generation, selective and potent TRPV1 antagonist in *in vivo* models that are relevant to humans." Szallasi et. al. *TRENDS in Molecular Medicine* **2006**, *12*, 545-554

With respect to COPD and the references submitted again the examiner submits that the administration of capsaicin and the antagonism of the capsaicin induced response, is not

physiologically correlated with this disease. However we do not even have this type of data before us here. It is very clear that the cell based assays do not correlate with treatment, and in general neither do animal assays. In the instant case, given the total lack of predictability and the paucity of data provided a lack of enablement was entirely appropriate and is maintained.

The rejections for enablement with respect to how to make and use the compounds the rejection is maintained in part and with drawn in part. As per the telephone interview, many of the arguments presented in the remarks are moot. The prophetic syntheses are just that and from a practical point of view are of little value.

The number of examples provided by the specification are few and have been discussed previously (and are reproduced here again). It would appear that the applicant is arguing that essentially any molecule, even molecules of unknown structure, can be made without undue experimentation. This is in fact not the situation in the chemical arts.

As stated in the preface to a recent treatise:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team

of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) [preface].....even structurally simple compounds often turn out not to be so easy to make as initially thought. [pg. 2]..... As illustrated by the examples discussed below, a good retrosynthesis requires much synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures [pg. 3]..... As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural features of a given starting material, and unexpected products may readily be formed. [8].....Even the most experienced chemist will not be able to foresee all potential pitfalls of a synthesis, specially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even simple chemical transformations can no longer be performed. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity [pg. 9]....." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface pg. 1-15. **(E)**

The examiner failed to notice that a large excess of piperidine was used in the SNAr reaction which of course can act as a base, thus no additional base is needed. The examiner apologizes for this clear oversight. With respect to the need for an activating group in ortho or para position in the SNAr reaction of the fluoronitriles, the examiner stands corrected as evidenced by the recent discovery of somewhat forcing conditions for the reaction of meta-nitriles (cited by applicant Tetrahedron, 1999, 55:13285-13300), however the reactions of meta substituted compounds are unpredictable as stated by the applicant remarks at 30: "Exhibit M notes that the following proposed reaction had a **zero percent yield**" (referring to the reaction of a meta substituted nitrile). While no doubt the entire scope of the claims is not enabled, the main point of contention after the telephone interview was the nature of the substituent amino heterocycle (NR2R3). The examiner has been accused of taking official notice on the how to use requirement of 112 1st paragraph with respect to the compounds, a more detailed analysis will be included in the maintained rejection below.

A recent ruling by the Federal circuit discusses enablement in the context of the automotive art, but there is little difference in the position of the court and the position of the examiner instant case, ATI v. BMW et. al. (Fed. Cir. 2007):

> "We also reject ATI's argument that because the specification enables one mode of practicing the invention, viz., mechanical side impact sensors, the enablement requirement is satisfied. We addressed and rejected a similar argument made in Liebel-Flarsheim Co. v. Medrad, Inc., 481 F.3d 1371 (Fed. Cir. 2007). In that case, the invention was a front-loading fluid injector system with a replaceable syringe capable of at 1373. We construed the asserted claims, as urged by the patentee, to include an injector with and without a pressure jacket. Although the specification clearly enabled an injector with a pressure jacket, we concluded that it did not enable an injector without such a jacket and that the claims were invalid for lack of enablement. at 1379. We stated that there "must be 'reasonable enablement of the scope of the range' which, in this case, includes both injector systems with and without a pressure jacket." withstanding high pressure for delivering a contrast agent to a patient. Id. Id. Id. at 1380 (internal citation omitted).
> Similarly, in this case, the claim construction of the relevant claim limitation resulted in the scope of the claims including both mechanical and electronic side impact sensors. Disclosure of only

> mechanical side impact sensors does not permit one skilled in the art to make and use the invention as broadly as it was claimed, which includes electronic side impact sensors. Electronic side impact sensors are not just another known species of a genus consisting of sensors, but are a distinctly different sensor compared with the well-enabled mechanical side impact sensor that is fully discussed in the specification. Thus, in order to fulfill the enablement requirement, the specification must enable the full scope of the claims that includes both electronic and mechanical side impact sensors, which the specification fails to do.
> We stated in Liebel: "The irony of this situation is that Liebel successfully pressed to have its claims include a jacketless system, but, having won that battle, it then had to show that such a claim was fully enabled, a challenge it could not meet." Id. at 1380. ATI sought to have the scope of the claims of the '253 patent include both mechanical and electronic side impact sensors. It succeeded, but then was unable to demonstrate that the claim was fully enabled. Claims must be enabled to correspond to their scope."

One of the double patenting rejections is withdrawn since the case is now gone abandoned. The remaining double patenting rejections are maintained for the reasons of record, since the '848 and '27 applications have common inventors regardless of the assignment. This action is made **FINAL**.

Objections

4. Claim 4 is objected to for depending from a rejected base claim, but would be allowable if put in proper dependent format.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-3, 5 & 7, 20, 23, 25, 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a handful of compounds that might be useful in treating pain, it does not reasonably provide enablement for the excessively protracted list of compounds and diseases claimed. The specification does not enable any person skilled in the art

to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a variety of substituted phenyl derivatives, heterocycles, and amines bearing multiple substitutions, as well using these compounds for treating a myriad of diseases. **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds. In addition these compounds are claimed to be used as drugs. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic chemist who would make the compounds. Presumably a Medical Doctor, Veterinarian or Pharm. D. would use the compounds to treat humans or animals. **(C) The state of the prior art:** Little prior art exists on these complex compounds, however the synthesis will be evaluated on what is known using scientific principles. Certain TRPV1 antagonists are known to be useful in treating pain. **(E) The level of predictability in the art:** Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3. Medicinal chemistry is also unpredictable **(F) The amount of direction provided by the inventor, (G)**

The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention: Claims 1 and 2 recite groups that are unknown to the examiner (1,3,2-dithiazocane 1,3,2-dithiazepane) or heretofore theoretical molecules (1,3,2-dioxazetidine and 1,3,2-dithiazetidine) Figure 1.

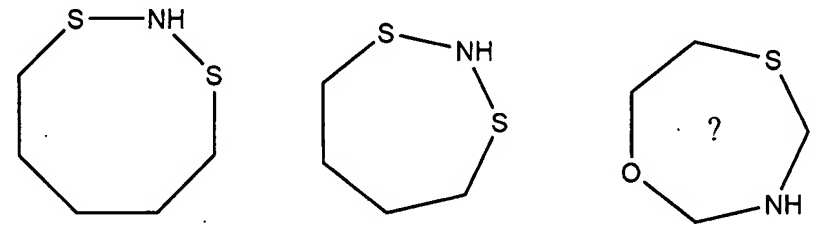

Figure 1. Possibilities for R2 and R3?

While it is very clear that no one can make the scope of the invention. The directions that one would give to the synthetic chemist who would make these compounds are insufficient. No chemist would understand how to make, "R2 and R3 together with the nitrogen atom to which they are attached, form a 3-8 membered saturated heterocyclic ring optionally interrupted by one or two atoms selected from the group consisting of oxygen, sulfur and nitrogen.". While the applicant submits that this is "standard language", no chemist would recognize this as standard language. The examiner maintains that this is in fact unreasonable, nonstandard language that is not found in books on heterocyclic chemistry. In addition, no one can use the full scope of the invention. The applicant has given the public little guidance as to what these compounds do in

the physiological sense. The sole statement we are given: "For practical reasons, the compounds are grouped in four classes of activity as follows: IC50- A < or = 0.11μM B < or = 0.5μM C < or = ~ 1μM < D The compounds of the present invention also show excellent selectivity, and strong activity in other assays 2-5 described above." A mention of "selectivity" is given. Is this a reference to activity at the putative purinergic receptor? From an examination of the trends given in Table 1 it is clear that a very minor change in the structure of the antagonist results in dramatic changes in activity. For example a bioisosteric replacement of the 4-methylene group of piperidine (Example 1-1) with an NH as in piperazine Example I-25 results in compounds with a at least a 10 fold decrease in activity. The compounds of broad claims of 1-3, 5-7, would likely not work as antagonists. It would appear the benzyl group should bear a lipophilic moiety like trifluoromethyl or OiPr. Certainly we cannot expect compounds containing sulfur or various optional substituents to function as antagonists even if they could be prepared. The applicant has argued that the structure of the compounds does not matter and that the examiner is taking official notice of the fact that the structure of the compound is crucial for activity. The submission of U.S. patent 5,453,426 by the applicant, which discloses adenosine antagonists is completely off the mark since in fact the instant claims are directed towards ligands at TRPV1, the adenosine receptor is not even in the same type of protein (it is a GPCR TRPV1 is an ion channel). The examiner would like clarification and a statement of the relevance of U.S. patent 5,453,426 and an explanation of how adenosine receptor antagonists and the instantly claimed compounds are related. To further clarify and make the record clear that the examiner is not taking official notice even though it is a fundamental precept of medicinal chemistry that hardly needs repeating that the structure of a compound is critical for activity, the examiner submits:

Martin, Yvonne C. et. al. "Do Structurally Similar Molecules Have Similar Biological Activity?" *Journal of Medicinal Chemistry* **2002**, *45*, 4350-4358:

"..... compounds that look very similar to a chemist sometimes bind in very different orientations in the protein active site, bind to a different conformation of a protein, or bind to a different protein altogether.[15] In fact, such observations are why medicinal chemists need to make so many compounds to optimize the biological activity of a structural class, even when they are designing to a biological target of known structure...(pg. 4536 column 2, line 9).....This work also shows that the biological similarity is not so strong as has previously been assumed. For example, at $\geq$ 0.85 Tanimoto similarity in Daylight fingerprints, **only 30% of compounds similar to an active are themselves active**."(conclusions)

More informatively, a large SAR study was done on TRPV1 antagonist remarkably similar to the compounds of the instant case, which no doubt benefited the design of the instant invention, Swanson et. al. "Identification and Biological Evaluation of 4-(3-Trifluoromethylpyridin-2-yl)piperazine-1-carboxylic Acid (5-Trifluoromethylpyridin-2-yl)amide, a High Affinity TRPV1 (VR1) Vanilloid Receptor Antagonist" *Journal of Medicinal Chemistry* **2005**, 48, 1857-1872. In this study it was found that the heterocyclic moiety must be a piperidine, or piperazine:

> "The first library (Figure 1) demonstrated the desirability of an electron-withdrawing group in the para position of the aniline fragment for antagonist activity and suggested that 3-substituted pyridin-2- ylpiperazines were favored. In the second library (Figure 2) which contained no 3-substituted pyridines only low affinity agonists and antagonists were obtained. The third library (Figure 3) was most informative and clearly demonstrated the importance of a 3-substituted pyridin- 2-ylpiperazine (3-Cl, 3-CH3, and 3-CF3) and a *p*-trifluoromethyl group in the aniline fragment. A fourth library, not shown, prepared from aliphatic isocyanates and 3-substituted pyridin-2-ylpiperazines afforded only inactive compounds, suggesting the need for an aromatic urea. With the intrinsic activity of the pyridinylpiperazine template confirmed, we turned our attention to a more thorough investigation of SAR at the human receptor via targeted synthesis. To this end, specific changes to the pyridine, piperazine, and aniline fragments were made. When the pyridine point of attachment was examined, 17 and 18, it was immediately apparent that the pyridin-2-ylpiperazine was optimal. A range of modifications to or replacements for the piperazine (20-26) showed that the piperazine ring was tolerant of small substituents (e.g. 20) but further substitution (21-23), ring expansion (24) or replacement with 3-aminopyrrolidine (25) or 4-aminopiperidine (26) afforded considerably less active compounds. Removal of a

> single piperazine nitrogen (27 and 28), using the chemistry of Scheme 2, afforded a less active compound as did removal of both a piperazine and the pyridine nitrogens, using the chemistry of Scheme 3 (29 and 30)."

Compounds 23 and 25, are inactive, not less active, but inactive.

Table 1. Potency at Recombinant TRPV1[a]

compd	human EC_{50} (nM)	efficacy (%)	human IC_{50} (nM)	SEM (n)	rat EC_{50} (nM)	efficacy (%)	rat IC_{50} (nM)
23			>10000	(3)			>10000
25	>10000, IA[b]		>10000	(3)			13100

What are the important structural features for the claimed utility? The compounds that were prepared at least, a lipophilic substituents of limited size were used at R4 in addition the aminoheterocycle and R4 are never in the ortho position, and only a limited identity of the heterocycle. Note that trifluoromethyl OiPr is present in all compounds, and this substitution would seem to be required. In this case the claimed compounds bear no structural resemblance to one the ones actually prepared.

The pharmacology of TRPV1 is complex, with the receptor expressed both centrally and peripherally. It is worth pointing out that while capsaicin is an effective tool as agonist when doing high-throughput pharmacology, it is not the endogenous ligand for TRPV1. Protons and heat and possibly a few lipids are thus far the only known endogenous ligands for this receptor. Is this antagonism competitive or non-competitive? We do not know. While these compounds are reported to have "strong activity" the language employed in the specification (not past tense) suggests that these experiments were either being performed or were not performed at the time of

filing. Regardless for pain treatment we have only rat DRG data to rely upon and as pointed out by Szallasi et. al. *TRENDS in Molecular Medicine* **2006**, *12*, 545-554:

> "Given the species-related differences in both the neurochemistry of capsaicin-sensitive neurons [2] and the pharmacological properties of TRPV1 [99], one should exercise utmost caution when extrapolating results obtained in rodents to humans."

So while potentially useful for treating pain in some rodents, we cannot believe that these compounds would be useful for treating pain in humans. The species variation of the receptor in mammals is quite significant as has been summarized by Ohta et. al. *Biochemical Pharmacology* **2005**, *71*, 173-187, pg. 174 column 1:

> "There are some notable species differences in the compound sensitivities of these channels. For instance, capsaicin has an agonistic action in most mammalian orthologues except for rabbit TRPV1 [12]. Indeed, rabbit dorsal root ganglion (DRG) neurons are resistant to the acute toxicity of capsaicin [18] and have no resiniferatoxin-binding site [19]. Furthermore, human [10] and guinea-pig TRPV1 [11] have little sensitivity to PPAHV, while rat [10,20], mouse [13] and dog TRPV1 [14] are significantly sensitive to PPAHV. RTX is more potent than olvanil in guinea-pig TRPV1 [11], but it is the opposite in other species [13–15,20]. Capsazepine, a TRPV1 antagonist, inhibits the response to acidic pH in human [10] and guinea-pig TRPV1 [11], but not in rat [10] and mouse TRPV1 [13]. For studying pain research in vivo, a number of reports have been published using rodent models. However, because of the inability of capsazepine to inhibit all modes of rat and mouse TRPV1 activation, it is suggested that use of a rodent

> model for studying TRPV1 antagonists may not accurately reflect the role of TRPV1 in human pathophysiology [13]."

It is abundantly clear that rabbits will not benefit from a molecule that antagonizes the effects of capsaicin since they lack sensitivity to capsaicin. In addition, the animal models chosen will not accurately predict the use of these compounds in humans. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a):

"A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)."

It is very clear that one could not make or use this very broad invention that has few working examples in this unpredictable art without undue experimentation.

6. Claims 19, 21, 22, 24, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims drawn toward inflammatory diseases and urological disorders are not enabled. The aforementioned discussion of the species differences in the TRPV1 receptor applies here, *vide supra*. Apparently some interest in TRPV1 antagonists as COPD and asthma treatments has revealed promising results as evidenced by the most recent study available to the examiner (Skogvall, S. et. al. *Pulmonary Pharmacology and Therapeutics* **2007**, 20, 273-280, pg. 279 column 2, to p.g 280) however the author expresses the view that the results with the canonical TRPV1 antagonist in tissue must be translated to in-vivo effects:

> "Hence, a novel principle such as the present capsazepinoids that reliably inhibit contractile effects **may be a useful** addition to the presently available drugs to treat diseases such as asthma and COPD. Since COPD and to a significant extent asthma may be considered small airways diseases [22,23] it is of particular interest that the present compounds exhibit efficacy in human small bronchi. Indeed, since previous work involving animal studies [4,16,24] has failed to identify the general bronchorelaxing properties of capsazepine the present discovery apparently required the use of human bronchial preparations as a primary study approach.
> In conclusion, capsazepine and some closely related analogues have been found to inhibit human small airway responsiveness to contractile mediators. If potency can be further increased **and the results translated to in vivo,** compounds representing this novel class of bronchorelaxants might become useful in the treatment of patients suffering from asthma and COPD. The present results thus stress the need of structure–activity relationship studies for this class of compounds as well as further investigations into their mechanism of action." Emphasis added.

In the instant case, these are very different compounds that were not tested in tissues (other than Chinese Hampster Ovary cells). With respect to overactive bladder, we must come to the conclusion that this area is highly unpredictable as stated by Szallasi et. al. (ibid.):

> "Despite the mounting evidence that suggests a

therapeutic value for TRPV1 antagonists in the symptomatic treatment of interstitial cystitis (IC), a word of caution seems reasonable at the moment. Resiniferatoxin (RTX) has been assayed intravesically in IC patients with the expectation that TRPV1 desensitization should be able to decrease both pain and urinary frequency. The results of the two available placebo-controlled clinical trials are conflicting: one suggests clinical utility [73], whereas the other does not demonstrate any advantage from TRPV1 desensitization [74]. Patients with neurogenic and non-neurogenic forms of detrusor overactivity, in contrast with IC patients, responded positively to intravesical RTX.....**Therefore, the effect of a strong TRPV1 antagonist on urinary frequency and incontinence of patients with detrusor overactivity is still unpredictable.**" Emphasis added.

As per the MPEP 2164.04:

While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection.
The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. This can be done by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact. For example, doubt may arise about enablement

> because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation. In such a case, the examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. See MPEP § 2164.06(a). References should be supplied if possible to support a *prima facie* case of lack of enablement, but are not always required. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). However, specific technical reasons are always required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-3, 5, 7, 19-26 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-4, 8-20 of copending Application No. 10/513,848. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application and the referenced copending application would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The Markush structures of the copending application have significant overlap with those of the instant case. The method claims from which they depend are essentially the same.

8. Claims 1-3, 5, 7, 19-26 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-4, 6-22 of copending Application No. 10/575,027. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application and the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The Markush structures of the copending application have significant overlap with those of the instant case. The method claims from which they depend are essentially the same.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Rita Desai can be reached on (571) 272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

R Desai
11/26/07

RITA DESAI
PRIMARY EXAMINER